CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074727

Trade Name : ACYCLOVIR 200MG CAPSULES

Generic Name: Acyclovir 200mg Capsules

Sponsor : Mylan Pharmacueticals, Inc.

Approval Date: April 22, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074727

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074727

APPROVAL LETTER

ANDA 74-727

APR 22 1997

Mylan Pharmaceuticals Inc.
Attention: John P. O'Donnell, Ph.D.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Sir:

This is in reference to your abbreviated new drug application dated August 10, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Acyclovir Capsules, 200 mg.

Reference is also made to your amendments dated December 7, 1995, February 9, and June 13, 1996, February 13, 1997 and April 15, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Acyclovir Capsules, 200 mg to be bioequivalent and, therefore, therapeutically equivalent to those of the listed drug (Zovirax^{R} Capsules, 200 mg, of Glaxo Wellcome Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

4-22-97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074727

FINAL PRINTED LABELING

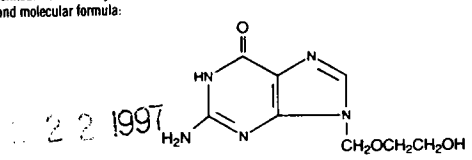
ACYCLOVIR CAPSULES
200 mg

SPECIMEN

ACY:R2

DESCRIPTION: Acyclovir is an antiviral drug. Each capsule, for oral administration, contains 200 mg of acyclovir. In addition, each capsule contains the following inactive ingredients: colloidal silicon dioxide, gelatin, magnesium stearate, pharmaceutical glaze, pregelatinized starch, propylene glycol, silicon dioxide, sodium lauryl sulfate, synthetic black iron oxide, titanium dioxide, FD&C Blue #1, FD&C Red #3, D&C Yellow #10 Aluminum Lake, FD&C Blue #1 Aluminum Lake, FD&C Blue #2 Aluminum Lake, and FD&C Red #40 Aluminum Lake.

The chemical name of acyclovir is 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]-6*H*-purin-6-one. It has the following structural and molecular formula:



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$C_8H_{11}N_5O_3$

Acyclovir is a white, crystalline powder with a molecular weight of 225.21, and a maximum solubility in water of 2.5 mg/mL at 37°C.

CLINICAL PHARMACOLOGY: Mechanism of Antiviral Effects: Acyclovir is a synthetic purine nucleoside analogue with *in vitro* and *in vivo* inhibitory activity against human herpes viruses including herpes simplex types 1 (HSV-1) and 2 (HSV-2), varicella-zoster virus (VZV), Epstein-Barr virus (EBV) and cytomegalovirus (CMV). In cell culture, acyclovir has the highest antiviral activity against HSV-1, followed in decreasing order of potency against HSV-2, VZV, EBV and CMV.[1]

The inhibitory activity of acyclovir for HSV-1, HSV-2, VZV, and EBV is highly selective. The enzyme thymidine kinase (TK) of normal uninfected cells does not effectively use acyclovir as a substrate. However, TK encoded by HSV, VZV, and EBV[2] converts acyclovir into acyclovir monophosphate, a nucleotide analogue. The monophosphate is further converted into diphosphate by cellular guanylate kinase and into triphosphate by a number of cellular enzymes.[3] Acyclovir triphosphate interferes with herpes simplex virus DNA polymerase and inhibits viral DNA replication. Acyclovir triphosphate also inhibits cellular α-DNA polymerase, but to a lesser degree. *In vitro*, acyclovir triphosphate can be incorporated into growing chains of DNA by viral DNA polymerase and to a much smaller extent by cellular α-DNA polymerase.[4] When incorporation occurs, the DNA chain is terminated.[5,6] Acyclovir is preferentially taken up and selectively converted to the active triphosphate form by herpesvirus-infected cells. Thus, acyclovir is much less toxic *in vitro* for normal uninfected cells because: 1) less is taken up; 2) less is converted to the active form; 3) cellular α-DNA polymerase is less sensitive to the effects of the active form. The mode of acyclovir phosphorylation in cytomegalovirus-infected cells is not clearly established, but may involve virally induced cell kinases or an unidentified viral enzyme. Acyclovir is not efficiently activated in cytomegalovirus infected cells, which may account for the reduced susceptibility of cytomegalovirus to acyclovir *in vitro*.

Microbiology: The quantitative relationship between the *in vitro* susceptibility of herpes simplex and varicella-zoster viruses to acyclovir and the clinical response to therapy has not been established in humans, and virus sensitivity testing has not been standardized. Sensitivity testing results, expressed as the concentration of drug required to inhibit by 50% the growth of virus in cell culture (ID_{50}), vary greatly depending upon the particular assay used,[7] the cell type employed,[8] and the laboratory performing the test.[1] The ID_{50} of acyclovir against HSV-1 isolates may range from 0.02 mcg/mL (plaque reduction in Vero cells) to 5.9 to 13.5 mcg/mL (plaque reduction in green monkey kidney [GMK] cells).[1] The ID_{50} against HSV-2 ranges from 0.01 mcg/mL to 9.9 mcg/mL (plaque reduction in Vero and GMK cells, respectively).[1]

Using a dye-uptake method in Vero cells,[9] which gives ID_{50} values approximately 5- to 10-fold higher than plaque reduction assays, 1417 HSV isolates (553 HSV-1 and 864 HSV-2) from approximately 500 patients were examined over a 5-year period.[10] These assays found that 90% of HSV-1 isolates were sensitive to ≤0.9 mcg/mL acyclovir and 50% of all isolates were sensitive to ≤0.2 mcg/mL acyclovir. For HSV-2 isolates, 90% were sensitive to ≤2.2 mcg/mL and 50% of all isolates were sensitive to ≤0.7 mcg/mL of acyclovir. Isolates with significantly diminished sensitivity were found in 44 patients. It must be emphasized that neither the patients nor the isolates were randomly selected and, therefore, do not represent the general population.

Most of the less sensitive HSV clinical isolates have been relatively deficient in the viral TK.[11-19] Strains with alterations in viral TK[20] or viral DNA polymerase[21] have also been reported. Prolonged exposure to low concentrations (0.1 mcg/mL) of acyclovir in cell culture has resulted in the emergence of a variety of acyclovir-resistant strains.[22]

The ID_{50} against VZV ranges from 0.17 to 1.53 mcg/mL (yield reduction, human foreskin fibroblasts) to 1.85 to 3.98 mcg/mL (foci reduction, human embryo fibroblasts [HEF]). Reproduction of EBV genome is suppressed by 50% in superinfected Raji cells or P3HR-1 lymphoblastoid cells by 1.5 mcg/mL acyclovir. CMV is relatively resistant to acyclovir with ID_{50} values ranging from 2.3 to 17.6 mcg/mL (plaque reduction, HEF cells) to 1.82 to 56.8 mcg/mL (DNA hybridization, HEF cells). The latent state of the genome of any of the human herpesviruses is not known to be sensitive to acyclovir.[1]

Pharmacokinetics: The pharmacokinetics of acyclovir after oral administration have been evaluated in 6 clinical studies involving 110 adult patients. In one uncontrolled study of 35 immunocompromised patients with herpes simplex or varicella-zoster infection, acyclovir capsules were administered in doses of 200 to 1000 mg every 4 hours, 6 times daily for 5 days, and steady-state plasma levels were reached by the second day of dosing. Mean steady-state peak and trough concentrations following the final 200 mg dose were 0.49 mcg/mL (0.47 to 0.54 mcg/mL) and 0.31 mcg/mL (0.18 to 0.41 mcg/mL), respectively, and following the final 800 mg dose were 2.8 mcg/mL (2.3 to 3.1 mcg/mL) and 1.8 mcg/mL (1.3 to 2.5 mcg/mL), respectively. In another uncontrolled study of 20 younger immunocompetent patients with recurrent genital herpes simplex infections, acyclovir capsules were administered in doses of 800 mg every 6 hours, 4 times daily for 5 days; the mean steady-state peak and trough concentrations were 1.4 mcg/mL (0.66 to 1.8 mcg/mL) and 0.55 mcg/mL (0.14 to 1.1 mcg/mL), respectively.

In general, the pharmacokinetics of acyclovir in children is similar to adults. Mean half-life after oral doses of 300 mg/m^2 and 600 mg/m^2, in children ages 7 months to 7 years, was 2.6 hours (range 1.59 to 3.74 hours).

In a multiple-dose crossover study where 23 volunteers received acyclovir as one 200 mg capsule, one 400 mg tablet, and one 800 mg tablet 6 times daily, absorption decreased with increasing dose and the estimated bioavailabilities of acyclovir were 20%, 15%, and 10%, respectively. The decrease in bioavailability is believed to be a function of the dose and not the dosage form. It was demonstrated that acyclovir is not dose proportional over the dosing range 200 mg to 800 mg. In this study, steady-state peak and trough concentrations of acyclovir were 0.83 and 0.46 mcg/mL, 1.21 and 0.63 mcg/mL, and 1.61 and 0.83 mcg/mL for the 200, 400, and 800 mg dosage regimens, respectively.

In another study in 6 volunteers, the influence of food on the absorption of acyclovir was not apparent.

Following oral administration, the mean plasma half-life of acyclovir in volunteers and patients with normal renal function ranged from 2.5 to 3.3 hours. The mean renal excretion of unchanged drug accounts for 14.4% (8.6% to 19.8%) of the orally administered dose. The only urinary metabolite (identified by high performance liquid chromatography) is 9-[(carboxymethoxy)methyl]-guanine. The half-life and total body clearance of acyclovir are dependent on renal function. A dosage adjustment is recommended for patients with reduced renal function (see DOSAGE AND ADMINISTRATION).

Orally administered acyclovir in children less than 2 years of age has not yet been fully studied.

INDICATIONS AND USAGE: Acyclovir capsules are indicated for the treatment of initial episodes and the management of recurrent episodes of genital herpes in certain patients.

Acyclovir capsules are indicated for the acute treatment of herpes zoster (shingles) and chickenpox (varicella).

Genital Herpes Infections: The severity of disease is variable depending upon the immune status of the patient, the frequency and duration of episodes, and the degree of cutaneous or systemic involvement. These factors should determine patient management, which may include symptomatic support and counseling only, or the institution of specific therapy. The physical, emotional, and psychosocial difficulties posed by herpes infections as well as the degree of debilitation, particularly in immunocompromised patients, are unique for each patient, and the physician should determine therapeutic alternatives based on his or her understanding of the individual patient's needs. Thus, orally administered acyclovir is not appropriate in treating all genital herpes infections. The following guidelines may be useful in weighing the benefit/risk considerations in specific disease categories:

First Episodes (primary and nonprimary infections-commonly known as initial genital herpes): Double-blind, placebo-controlled studies[23,24,25] have demonstrated that orally administered acyclovir significantly reduced the duration of acute infection (detection of virus in lesions by tissue culture) and lesion healing. The duration of pain and new lesion formation was decreased in some patient groups. The promptness of initiation of therapy and/or the patient's prior exposure to herpes simplex virus may influence the degree of benefit from therapy. Patients with mild disease may derive less benefit than those with more severe episodes. In patients with extremely severe episodes, in which prostration, central nervous system involvement, urinary retention, or inability to take oral medication require hospitalization and more aggressive management, therapy may be best initiated with intravenous acyclovir.

Recurrent Episodes: Double-blind, placebo-controlled studies[16,26-32] in patients with frequent recurrences (6 or more episodes per year) have shown that orally administered acyclovir given daily for 4 months to 3 years prevented or reduced the frequency and/or severity of recurrences in greater than 95% of patients.

In a study of 283 patients who received 400 mg (two 200 mg capsules) twice daily for 3 years, 45%, 52% and 63% of patients remained free of recurrences in the first, second, and third years, respectively. Serial analyses of the 3-month recurrence rates for the 283 patients showed that 71% to 87% were recurrence-free in each quarter, indicating that the effects are consistent over time.

The frequency and severity of episodes of untreated genital herpes may change over time. After 1 year of therapy, the frequency and severity of the patient's genital herpes infection should be re-evaluated to assess the need for continuation of therapy with acyclovir. Re-evaluation will usually require a trial of acyclovir to assess the need for reinstitution of suppressive therapy. Some patients, such as those with very frequent or severe episodes before treatment, may warrant uninterrupted suppression for more than a year.

Chronic suppressive therapy is most appropriate when, in the judgement of the physician, the benefits of such a regimen outweigh known or potential adverse effects. In general, orally administered acyclovir should not be used for the suppression of recurrent disease in mildly affected patients. Unanswered questions concerning the relevance to humans of *in vitro* mutagenicity studies and reproductive toxicity studies in animals given high parenteral doses of acyclovir for short periods (see PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility) should be borne in mind when designing long-term management for individual patients. Discussion of these issues with patients will provide them the opportunity to weigh the potential for toxicity against the severity of their disease. Thus, this regimen should be considered only for appropriate patients with annual re-evaluation.

Limited studies[31,32] have shown that there are certain patients for whom intermittent short-term treatment of recurrent episodes is effective. This approach may be more appropriate than a suppressive regimen in patients with infrequent recurrences.

Immunocompromised patients with recurrent herpes infections can be treated with either intermittent or chronic suppressive therapy. Clinically significant resistance, although rare, is more likely to be seen with prolonged or repeated therapy in severely immunocompromised patients with active lesions.

Herpes Zoster Infections: In a double-blind, placebo-controlled study of 187 normal patients with localized cutaneous zoster infection (93 randomized to acyclovir and 94 to placebo), acyclovir (800 mg 5 times daily for 10 days) shortened the times to lesion scabbing, healing, and complete cessation of pain, and reduced the duration of viral shedding and the duration of new lesion formation.[33]

In a similar double-blind, placebo-controlled study in 83 normal patients with herpes zoster (40 randomized to acyclovir and 43 to placebo), acyclovir (800 mg 5 times daily for 7 days) shortened the times to complete lesion scabbing, healing, and cessation of pain, reduced the duration of new lesion formation, and reduced the prevalence of localized zoster-associated neurologic symptoms (paresthesia, dysesthesia, or hyperesthesia).[34]

Chickenpox: In a double-blind, placebo-controlled efficacy study in 110 normal patients, ages 5 to 16 years, who presented within 24 hours of the onset of a typical chickenpox rash, acyclovir was administered orally 4 times daily for 5 to 7 days at doses of 10, 15, or 20 mg/kg depending on the age group. Treatment with acyclovir reduced the maximum number of lesions (336 vs. greater than 500; lesions beyond 500 were not counted). Treatment with acyclovir also shortened the mean time to 50% healing (7.1 days vs. 8.7 days), reduced the number of vesicular lesions by the second day of treatment (49 vs. 113), and decreased the proportion of patients with fever (temperature greater than 100° F) by the second day (19% vs. 57%). Treatment with acyclovir did not affect the antibody response to varicella-zoster virus measured 1 month and 1 year following the treatment.[35]

In two concurrent double-blind, placebo-controlled studies, a total of 883 normal patients, ages 2 to 18 years, were enrolled within 24 hours of the onset of a typical chickenpox rash, and acyclovir was administered at 20 mg/kg orally up to 800 mg 4 times daily for 5 days. In the larger study of 815 children ages 2 to 12 years, treatment with acyclovir reduced the median maximum number of lesions (277 vs. 386), reduced the median number of vesicular lesions by the second day of treatment (26 vs. 40), and reduced the proportion of patients with moderate to severe itching by the third day of treatment (15% vs. 34%).[36] In addition, in both studies (883 patients, ages 2 to 18 years), treatment with acyclovir also decreased the proportion of patients with fever (temperature greater than 100° F), anorexia, and lethargy by the second day of treatment, and decreased the mean

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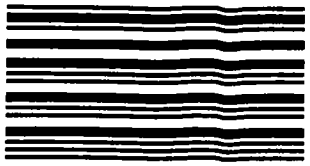

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Diagnosis: Diagnosis is confirmed by virus isolation. Accelerated viral culture assays or immunocytology allow more rapid diagnosis than standard viral culture. For patients with initial episodes of genital herpes, appropriate examinations should be performed to rule out other sexually transmitted diseases. While cutaneous lesions associated with herpes simplex and varicella-zoster infections are often characteristic, the finding of multinucleated giant cells in smears prepared from lesion exudate or scrapings may provide additional support to the clinical diagnosis.[39]

Multinucleated giant cells in smears do not distinguish varicella-zoster from herpes simplex infections.

CONTRAINDICATIONS: Acyclovir capsules are contraindicated for patients who develop hypersensitivity or intolerance to the components of the formulations.

WARNINGS: Acyclovir capsules are intended for oral ingestion only.

PRECAUTIONS: General: Acyclovir has caused decreased spermatogenesis at high parenteral doses in some animals and mutagenesis in some acute studies at high concentrations of drug (see PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility). The recommended dosage should not be exceeded (see DOSAGE AND ADMINISTRATION).

Exposure of herpes simplex and varicella-zoster isolates to acyclovir *in vitro* can lead to the emergence of less sensitive viruses. The possibility of the appearance of less sensitive viruses in humans must be borne in mind when treating patients. The relationship between the *in vitro* sensitivity of herpes simplex or varicella-zoster virus to acyclovir and clinical response to therapy has yet to be established (see CLINICAL PHARMACOLOGY: Microbiology).

Because of the possibility that less sensitive virus may be selected in patients who are receiving acyclovir, all patients should be advised to take particular care to avoid potential transmission of virus if active lesions are present while they are on therapy. In severely immunocompromised patients, the physician should be aware that prolonged or repeated courses of acyclovir may result in selection of resistant viruses which may not fully respond to continued acyclovir therapy.

Caution should be exercised when administering acyclovir to patients receiving potentially nephrotoxic agents since this may increase the risk of renal dysfunction.

Information for Patients: Patients are instructed to consult with their physician if they experience severe or troublesome adverse reactions, they become pregnant or intend to become pregnant, they intend to breastfeed while taking orally administered acyclovir, or they have any other questions.

Genital Herpes Infections: Genital herpes is a sexually transmitted disease and patients should avoid intercourse when visible lesions are present because of the risk of infecting intimate partners. Acyclovir capsules are for oral ingestion only. Medication should not be shared with others. The prescribed dosage should not be exceeded. Acyclovir does not eliminate latent viruses. Patients are instructed to consult with their physician if they do not receive sufficient relief in the frequency and severity of their genital herpes recurrences.

There are still unanswered questions concerning reproductive/gonadal toxicity and mutagenesis; long-term studies are continuing. Decreased sperm production has been seen at high doses in some animals; a placebo-controlled clinical study using 400 mg or 1000 mg of acyclovir per day for 6 months in humans did not show similar findings.[40] Chromosomal breaks were seen *in vitro* after brief exposure to high concentrations. Some other currently marketed medications also cause chromosomal breaks, and the significance of this finding is unknown. A placebo-controlled clinical study using 800 mg of acyclovir per day for 1 year in humans did not show any abnormalities in structure or number of chromosomes.[28]

Herpes Zoster Infections: Adults age 50 or older tend to have more severe shingles, and treatment with acyclovir showed more significant benefit for older patients. Treatment was begun within 72 hours of rash onset in these studies, and was more useful if started within the first 48 hours.

Chickenpox: Although chickenpox in otherwise healthy children is usually a self-limited disease of mild to moderate severity, adolescents and adults tend to have more severe disease. Treatment was initiated within 24 hours of the typical chickenpox rash in the controlled studies, and there is no information regarding the effects of treatment begun later in the disease course. It is unknown whether the treatment of chickenpox in childhood has any effect on long-term immunity. However, there is no evidence to indicate that treatment of chickenpox with acyclovir would have any effect on either decreasing or increasing the incidence or severity of subsequent recurrences of herpes zoster (shingles) later in life. Intravenous acyclovir is indicated for the treatment of varicella-zoster infections in immunocompromised patients.

Drug Interactions: Co-administration of probenecid with intravenous acyclovir has been shown to increase the mean half-life and the area under the concentration-time curve. Urinary excretion and renal clearance were correspondingly reduced.[41] The clinical effects of this combination have not been studied.

Carcinogenesis, Mutagenesis, Impairment of Fertility: The data presented below include references to peak steady-state plasma acyclovir concentrations observed in humans treated with 800 mg given orally 6 times a day (dosing appropriate for treatment of herpes zoster) or 200 mg given orally 6 times a day (dosing appropriate for treatment of genital herpes). Plasma drug concentrations in animal studies are expressed as multiples of human exposure to acyclovir at the higher and lower dosing schedules (see CLINICAL PHARMACOLOGY: Pharmacokinetics).

Acyclovir was tested in lifetime bioassays in rats and mice at single daily doses of up to 450 mg/kg administered by gavage. There was no statistically significant difference in the incidence of tumors between treated and control animals, nor did acyclovir shorten the latency of tumors. At 450 mg/kg/day, plasma concentrations were 3 to 6 times human levels in the mouse bioassay and 1 to 2 times human levels in the rat bioassay.

Acyclovir was tested in two *in vitro* cell transformation assays. Positive results were observed at the highest concentration tested (31 to 63 times human levels) in one system and the resulting morphologically transformed cells formed tumors when inoculated into immunosuppressed, syngeneic, weanling mice. Acyclovir was negative (40 to 80 times human levels) in the other, possibly less sensitive, transformation assay.

In acute cytogenetic studies, there was an increase, though not statistically significant, in the incidence of chromosomal damage at maximum tolerated parenteral doses of acyclovir (100 mg/kg) in rats (62 to 125 times human levels) but not in Chinese hamsters; higher doses of 500 and 1000 mg/kg were clastogenic in Chinese hamsters (380 to 760 times human levels). In addition, no activity was found after 5 days dosing in a dominant lethal study in mice (36 to 73 times human levels). In all 4 microbial assays, no evidence of mutagenicity was observed. Positive results were obtained in 2 of 7 genetic toxicity assays using mammalian cells *in vitro*. In human lymphocytes, a positive response for chromosomal damage was seen at concentra-

tions 150 to 300 times the acyclovir plasma levels achieved in humans. At one locus in mouse lymphoma cells, mutagenicity was observed at concentrations 250 to 500 times human plasma levels. Results in the other five mammalian cell loci follow: at 3 loci in a Chinese hamster ovary cell line, the results were inconclusive at concentrations at least 1850 times human levels; at 2 other loci in mouse lymphoma cells, no evidence of mutagenicity was observed at concentrations at least 1500 times human levels.

Acyclovir has not been shown to impair fertility or reproduction in mice (450 mg/kg/day, p.o.) or in rats (25 mg/kg/day, s.c.). In the mouse study, plasma levels were 9 to 18 times human levels, while in the rat study they were 8 to 15 times human levels. At a higher dose in the rat (50 mg/kg/day, s.c.), there was a statistically significant increase in post-implantation loss, but no concomitant decrease in litter size. In female rabbits treated subcutaneously with acyclovir subsequent to mating, there was a statistically significant decrease in implantation efficiency but no concomitant decrease in litter size at a dose of 50 mg/kg/day (16 to 31 times human levels). No effect upon implantation efficiency was observed when the same dose was administered intravenously (53 to 106 times human levels). In a rat peri- and postnatal study at 50 mg/kg/day s.c. (11 to 22 times human levels), there was a statistically significant decrease in the group mean numbers of corpora lutea, total implantation sites, and live fetuses in the F1 generation. Although not statistically significant, there was also a dose-related decrease in group mean numbers of live fetuses and implantation sites at 12.5 mg/kg/day and 25 mg/kg/day, s.c. The intravenous administration of 100 mg/kg/day, a dose known to cause obstructive nephropathy in rabbits, caused a significant increase in fetal resorptions and a corresponding decrease in litter size (plasma levels were not measured). However, at a maximum tolerated intravenous dose of 50 mg/kg/day in rabbits (53 to 106 times human levels), no drug-related reproductive effects were observed.

Intraperitoneal doses of 80 or 320 mg/kg/day acyclovir given to rats for 6 and 1 months, respectively, caused testicular atrophy. Plasma levels were not measured in the 1-month study and were 24 to 48 times human levels in the 6-month study. Testicular atrophy was persistent through the 4-week postdose recovery phase after 320 mg/kg/day; some evidence of recovery of sperm production was evident 30 days postdose. Intravenous doses of 100 and 200 mg/kg/day acyclovir given to dogs for 31 days caused aspermatogenesis. At 100 mg/kg/day plasma levels were 47 to 94 times human levels, while at 200 mg/kg/day they were 159 to 317 times human levels. No testicular abnormalities were seen in dogs given 50 mg/kg/day i.v. for 1 month (21 to 41 times human levels) and in dogs given 60 mg/kg/day orally for 1 year (6 to 12 times human levels).

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category C. Acyclovir was not teratogenic in the mouse (450 mg/kg/day, p.o.), rabbit (50 mg/kg/day, s.c. and i.v.), or in standard tests in the rat (50 mg/kg/day, s.c.). These exposures resulted in plasma levels 9 and 18, 16 and 106, and 11 and 22 times, respectively, human levels. In a non-standard test in rats, there were fetal abnormalities, such as head and tail anomalies, and maternal toxicity.[42] In this test, rats were given 3 s.c. doses of 100 mg/kg acyclovir on gestation day 10, resulting in plasma levels 63 and 125 times human levels. There are no adequate and well-controlled studies in pregnant women. Acyclovir should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus. Although acyclovir was not teratogenic in standard animal studies, the drug's potential for causing chromosome breaks at high concentration should be taken into consideration in making this determination.

Nursing Mothers: Acyclovir concentrations have been documented in breast milk in two women following oral administration of acyclovir and ranged from 0.6 to 4.1 times corresponding plasma levels.[43,44] These concentrations would potentially expose the nursing infant to a dose of acyclovir up to 0.3 mg/kg/day. Caution should be exercised when acyclovir is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients less than 2 years of age have not been adequately studied.

ADVERSE REACTIONS: ***Herpes Simplex: Short-Term Administration:*** The most frequent adverse events reported during clinical trials of treatment of genital herpes with orally administered acyclovir were nausea and/or vomiting in 8 of 298 patient treatments (2.7%) and headache in 2 of 298 (0.6%). Nausea and/or vomiting occurred in 2 of 287 (0.7%) patients who received placebo.

Less frequent adverse events, each of which occurred in 1 of 298 patient treatments with orally administered acyclovir (0.3%), included diarrhea, dizziness, anorexia, fatigue, edema, skin rash, leg pain, inguinal adenopathy, medication taste, and sore throat.

Long-Term Administration: The most frequent adverse events reported in a clinical trial for the prevention of recurrences with continuous administration of 400 mg (two 200 mg capsules) 2 times daily for 1 year in 586 patients treated with acyclovir were: nausea (4.8%), diarrhea (2.4%), headache (1.9%), and rash (1.7%). The 589 control patients receiving intermittent treatment of recurrences with acyclovir for 1 year reported diarrhea (2.7%), nausea (2.4%), headache (2.2%), and rash (1.5%).

The most frequent adverse events reported during the second year by 390 patients who elected to continue daily administration of 400 mg (two 200 mg capsules) 2 times daily for 2 years were headache (1.5%), rash (1.3%), and paresthesia (0.8%). Adverse events reported by 329 patients during the third year include asthenia (1.2%), paresthesia (1.2%), and headache (0.9%).

Herpes Zoster: The most frequent adverse events reported during three clinical trials of treatment of herpes zoster (shingles) with 800 mg of oral acyclovir 5 times daily for 7 to 10 days in 323 patients were: malaise (11.5%), nausea (8.0%), headache (5.9%), vomiting (2.5%), diarrhea (1.5%), and constipation (0.9%). The 323 placebo recipients reported malaise (11.1%), nausea (11.5%), headache (11.1%), vomiting (2.5%), diarrhea (0.3%), and constipation (2.4%).

Chickenpox: The most frequent adverse events reported during three clinical trials of treatment of chickenpox with oral acyclovir in 495 patients were: diarrhea (3.2%), abdominal pain (0.6%), rash (0.6%), vomiting (0.6%), and flatulence (0.4%). The 498 patients receiving placebo reported: diarrhea (2.2%), flatulence (0.8%), and insomnia (0.4%).

Observed During Clinical Practice: Based on clinical practice experience in patients treated with oral acyclovir in the U.S., spontaneously reported adverse events are uncommon. Data are insufficient to support an estimate of their incidence or to establish causation. These events may also occur as part of the underlying disease process. Voluntary reports of adverse events which have been received since market introduction include:

General: fever, headache, pain, peripheral edema, and rarely, anaphylaxis

Nervous: confusion, dizziness, hallucinations, paresthesia, seizure, somnolence (These symptoms may be marked, particularly in older adults.)

Digestive: diarrhea, elevated liver function tests, gastrointestinal distress, nausea

Hemic and Lymphatic: leukopenia, lymphadenopathy

Musculoskeletal: myalgia

Skin: alopecia, pruritus, rash, urticaria

Special Senses: visual abnormalities

Urogenital: elevated creatinine

OVERDOSAGE: Patients have ingested intentional overdoses of up to 100 capsules (20 g) of acyclovir, with no unexpected adverse effects.

Precipitation of acyclovir in renal tubules may occur when the solubility (2.5 mg/mL) in the intratubular fluid is exceeded. Renal lesions considered to be related to obstruction of renal tubules by precipitated drug crystals occurred in the following species: rats treated with i.v. and i.p. doses of 20 mg/kg/day for 21 and 31 days, respectively, and at s.c. doses of 100 mg/kg/day for 10 days; rabbits at s.c. and i.v. doses of 50 mg/kg/day for 13 days; and dogs at i.v. doses of 100 mg/kg/day for 31 days. A 6-hour hemodialysis results in a 60% decrease in plasma acyclovir concentration. Data concerning peritoneal dialysis are incomplete but indicate that this method may be significantly less efficient in removing acyclovir from the blood. In the event of acute renal failure and anuria, the patient may benefit from hemodialysis until renal function is restored (see DOSAGE AND ADMINISTRATION).

DOSAGE AND ADMINISTRATION: Treatment of Initial Genital Herpes: 200 mg (one 200 mg capsule) every 4 hours, 5 times daily for 10 days.

Chronic Suppressive Therapy for Recurrent Disease: 400 mg (two 200 mg capsules) 2 times daily for up to 12 months, followed by re-evaluation. See INDICATIONS AND USAGE and PRECAUTIONS for considerations on continuation of suppressive therapy beyond 12 months. Alternative regimens have included doses ranging from 200 mg 3 times daily to 200 mg 5 times daily.

Intermittent Therapy: 200 mg (one 200 mg capsule) every 4 hours, 5 times daily for 5 days. Therapy should be initiated at the earliest sign or symptom (prodrome) of recurrence.

Acute Treatment of Herpes Zoster: 800 mg (four 200 mg capsules) every 4 hours orally, 5 times daily for 7 to 10 days.

Treatment of Chickenpox: ***Children (2 years of age and older):*** 20 mg/kg per dose orally 4 times daily (80 mg/kg/day) for 5 days. Children over 40 kg should receive the adult dose for chickenpox.

Adults and children over 40 kg: 800 mg four times daily for 5 days.

Therapy should be initiated at the earliest sign or symptom of chickenpox to derive the maximal benefits of therapy.

Patients with Acute or Chronic Renal Impairment: Comprehensive pharmacokinetic studies have been completed following intravenous acyclovir infusions in patients with renal impairment. Based on these studies, dosage adjustments are recommended in the following chart for genital herpes and herpes zoster indications:

Normal Dosage Regimen	Creatinine Clearance (mL/min/1.73m^2)	Adjusted Dosage Regimen	
		Dose (mg)	Dosing Interval
200 mg every 4 hours	>10	200	every 4 hours, 5x daily
	0-10	200	every 12 hours
400 mg every 12 hours	>10	400	every 12 hours
	0-10	200	every 12 hours
800 mg every 4 hours	>25	800	every 4 hours, 5x daily
	10-25	800	every 8 hours
	0-10	800	every 12 hours

Hemodialysis: For patients who require hemodialysis, the mean plasma half-life of acyclovir during hemodialysis is approximately 5 hours. This results in a 60% decrease in plasma concentrations following a 6-hour dialysis period. Therefore, the patient's dosing schedule should be adjusted so that an additional dose is administered after each dialysis.[45,46]

Peritoneal Dialysis: No supplemental dose appears to be necessary after adjustment of the dosing interval.[47,48]

HOW SUPPLIED: Acyclovir Capsules are available containing 200 mg of acyclovir in a lavender opaque capsule imprinted with MYLAN over 2200 in black ink on the body and cap. They are available as follows:

NDC 0378-2200-01
bottles of 100 capsules
NDC 0378-2200-05
bottles of 500 capsules

STORE AT 15° - 25°C (59° - 77°F).

PROTECT FROM LIGHT AND MOISTURE.

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

CAUTION: Federal law prohibits dispensing without prescription.

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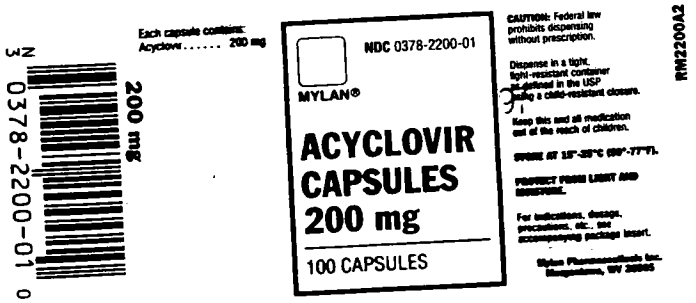
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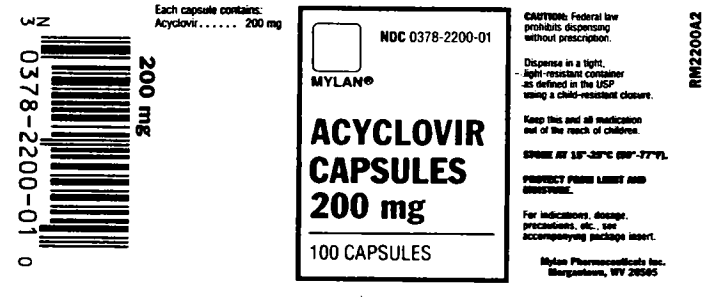
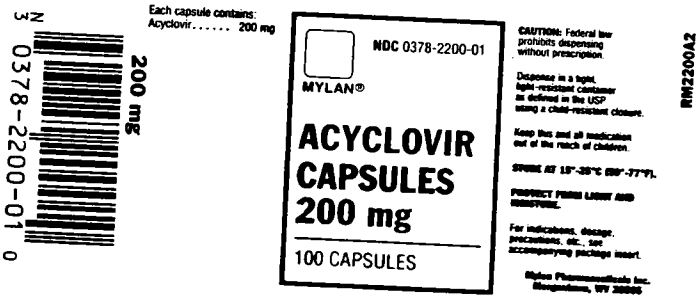
Morgantown, WV 26505
RM2200A2


Each capsule contains:
Acyclovir..... 200 mg
N 3 0378-2200-01 0
200 mg
NDC 0378-2200-01
MYLAN®
ACYCLOVIR
CAPSULES
200 mg
100 CAPSULES
CAUTION: Federal law prohibits dispensing without prescription.
Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.
Keep this and all medication out of the reach of children.
STORE AT 15°-25°C (59°-77°F).
PROTECT FROM LIGHT AND MOISTURE.
For indications, dosage, precautions, etc., see accompanying package insert.
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505
RM2200A2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For indications, dosage, precautions, etc., see accompanying package insert.
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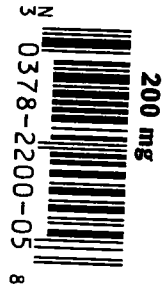
Morgantown, WV 26505
RM2200A2

Each capsule contains:
Acyclovir . . . . . 200 mg



NDC 0378-2200-05

MYLAN®

ACYCLOVIR CAPSULES 200 mg

500 CAPSULES

CAUTION: Federal law prohibits dispensing without prescription.

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Keep this and all medication out of the reach of children.

STORE AT 15°-25°C (59°-77°F).

PROTECT FROM LIGHT AND MOISTURE.

For indications, dosage, precautions, etc., see accompanying package insert.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RM220082

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074727

CHEMISTRY REVIEW(S)

ANDA APPROVAL SUMMARY

ANDA: 74-727

DRUG PRODUCT: Acyclovir Capsules

FIRM: Mylan Pharmaceutical Inc.

DOSAGE FORM: Capsules

STRENGTHS: 200 mg

CGMP STATEMENT/EIR UPDATE STATUS:

Manufacturer-Finished Dosage Form :

Mylan Pharmaceuticals Inc.
P.O. Box 4310
781 Chestnut Ridge Road
Morgantown, WV 26504-4310

***Note:** The updated and pre-approval EER was OK on 7-10-96

Manufacturer-Active Ingredients:

Note: The updated and pre-approval EER was OK on 7-10-96.

BIO STUDY:

The in vivo bioequivalence study and in vitro dissolution testing for the 200 mg capsule (Lot #2A005D) was found acceptable by L. Chuang reviewed on 5-20-96

VALIDATION -(DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):

Active Ingredient: N/A, product is compendial refer to memo dated 11/14/90 regarding Compliance Program Guidance Manual # 7346.832, code 52832 for ANDAs and AADAs.

Samples for the finish dosage form were picked up by Baltimore district representative on April 10, 1996 and found acceptable on June 11, 1996.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?:

Stability protocol: Satisfactory
Expiration Dating:
2 years expiration date with 1, 2 and 3 month accelerated stability data (37°C/75% R.H.) and 3,6,9,12,18,& 24 months room temperature at 25°C - 30°C (27.5°C ± 2.5°C) stability data on lot #2A005D for 100's (120 cc) and 500's (18 oz.).

1. CHEMISTRY REVIEW NO. 3

2. ANDA 74-727

3. NAME AND ADDRESS OF APPLICANT

Mylan Pharmaceutical Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

4. LEGAL BASIS FOR SUBMISSION

The applicant certifies , that to the best of it knowledge, U.S. Patent No. 4,199,574 will expire on April 22, 1997, a New Chemical Entity exclusivity period expired on March 29, 1992, an indication of acute treatment of varicella zoster virus expired on April 26, 1993 and the indication of varicella infections (chickenpox) will expire on February 26, 1995. The applicant will not claim an indication of varicella infections (chickenpox) until the expiration of this exclusivity period on February 26, 1995. Furthermore, the product will not be made available for sale until the expiration of U.S. Patent No. 4,199,574 on April 22, 1997.

Innovator: Burroughs Wellcome - Zovirax®

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Acyclovir

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

Firm:

8-10-95: Original
6-13-96: Amendment
2-13-97: Facsimile amendment
4-15-97: Telephone amendment

FDA:

9-19-95: Acknowledgement
4-17-96: 1st NA letter
2-4-97: 2nd NA letter

10. PHARMACOLOGICAL CATEGORY

Antiviral

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM

Capsule

14. POTENCY

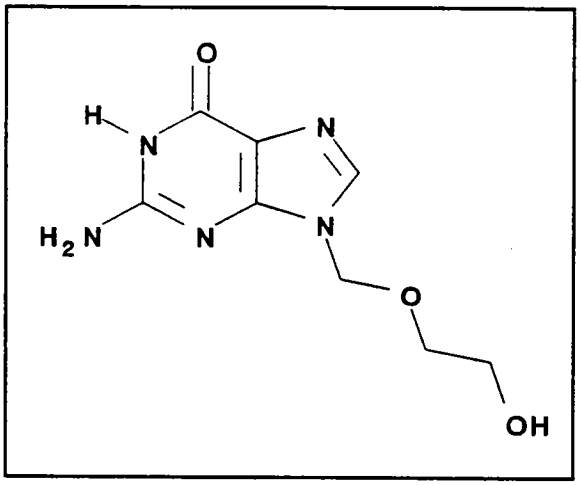
200 mg

15. CHEMICAL NAME AND STRUCTURE

Acyclovir USP

$C_8H_{11}N_5O_3$; M.W. = 225.21

CAS [59277-89-3]



1. 9-[(2-Hydroxyethoxy)methyl]guanine.

2. 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)-methyl]-

USP: White to off-white crystalline powder. Melts at temperatures higher than 250°, with decomposition. Soluble in 0.1 N hydrochloric acid; sparingly soluble in water; insoluble in alcohol.

Merck: Crystals from methanol, mp 256.5° - 257°. LD_{50} in mice (mg/kg): > 10,000 orally; 1000 i.p.

16. RECORDS AND REPORTS

N/A

17. COMMENTS

Q: 1. Please note the typographical error on page 6 (qualitative composition statement) in designating your footnote "[4]Black Imprinting inks" . Please revise and resubmit.

A: OK (see response 1 and Attachment A or page 7R of 2-13-97 amendment).

Q: 2. We concur that the high active content of the finished dosage form reduces the need for testing. However, we recommend that you include specifications for the in the blank batch record until you gain sufficient experience with this product. The in-process test may then be deleted through a supplemental application.

A: OK (see response 2 and Attachments B & C of 2-13-97 amendment).

Q: 3. We note the dissolution specifications in the revised stability data reports in Attachment D of the June 13, 1996 are listed as NLT [redacted] (O) in 30 minutes. Please revise to include the dissolution specification recommended by Division of Bioequivalence in the stability data reports.

A: OK (see response 3 and Attachments D of 2-13-97 amendment).

Status:

a. **EER: Satisfactory**

Requested for Mylan by L Tang on August 29, 1995 and found acceptable on 4-12-96.

b. **MV** (method validation): **Satisfactory**

Drug dosage form is not compendial. Method validation for finished product and samples for the finish dosage form were picked up by Baltimore District Representative on April 10, 1996 and found acceptable on June 11, 1996.

c. **Bio-Review: Satisfactory**

Satisfactory per L. Chuang reviewed on 5-20-96.

d. **Labeling review: Satisfactory or Pending**

Satisfactory per J. White reviewed on 2-?-97.

e. **DMFs: Satisfactory**

The May 1, 1996 amendment for has been reviewed and found acceptable per G. Smith on 9-11-96.

18. CONCLUSIONS AND RECOMMENDATIONS

Not Approvable (Minor)

19. REVIEWER: DATE COMPLETED:

Lucia C. Tang 2-20-97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074727

BIOEQUIVALENCE REVIEW(S)

D.J

ANDA 74-727

Mylan Pharmaceuticals, Inc.
Attention: Patrick K. Noonan, Ph.D.
781 Chestnut Ridge Road
P.O. BOX 4310
Morgantown WV 26504-4310

MAY 20 1996

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Acyclovir Capsules 200 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be conducted in 900 mL of distilled water at 37°C using USP 23 apparatus 1 (basket) at 100 rpm. The test products should meet the following specifications:

   Not less than of the labeled amount of acyclovir in the dosage form is dissolved in 30 minutes.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/ Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

9.N

MAY 20 1996

Acyclovir
200 mg Capsule
ANDA 74-727
Reviewer: L. Chuang

Mylan Pharmaceuticals Inc.
Morgantown, WV
Submission Date:
February 9, 1996

Review of an Amendment to a Bioequivalence Study and Dissolution Data

The original submission of this fasting bioequivalence study was found to be incomplete due to the following 4 deficiencies. This amendment contains the sponsor's responses.

1. The firm should provide the time period of medication and diet restrictions in the protocol and explanation for the 5 subjects who did not complete the study.

   The firm referred to the study medications and meals during the study as described in the original submission. The time frame of the diet and medication restrictions prior to the study are still not provided.

   This is, however, a minor concern of the reviewer and will not affect the acceptance of the study.

2. The firm should provide pre-study validation data for the assay methodology of acyclovir.

3. The firm should provide information on the assay methodology conducted for the dissolution tests and change the specification of the dissolution test to "not less than lissolved in 30 minutes".

   The firm described the assay methodology conducted for the dissolution tests as

   The specification of the dissolution test was changed to "NLT n 30 minutes".

4. The firm should conduct a limited food study.

   A limited food study has been conducted and submitted on 12/07/95. It was found to be acceptable by the Division of Bioequivalence on 05/09/96.

Comment:

The firm's responses, though not complete, are acceptable.

Recommendation:

1. The bioequivalence study conducted by Mylan Pharmaceuticals Inc. on its Acyclovir 200 mg capsule, Lot #2A005D, comparing to Zovirax^{R} 200 mg capsule, lot #3Z2158, manufactured by Burroughs Wellcome Co., in fasting volunteers, has been found acceptable by the Division of Bioequivalence. The study demonstrated that Mylan's acyclovir 200 mg capsule is bioequivalent to the reference product, Zovirax^{R} 200 mg capsule manufactured by Burroughs Wellcome Co. when administered under fasting condition.

   The bioequivalence study conducted by Mylan Pharmaceuticals Inc. on the same test and reference products as in the fasting study, but in non-fasting volunteers, has also been found acceptable by the Division of Bioequivalence on 05/09/96. The study demonstrated that Mylan's acyclovir 200 mg capsule is bioequivalent to the reference product, Zovirax^{R} 200 mg capsule manufactured by Burroughs Wellcome Co. when administered under non-fasting condition.

2. The dissolution tests conducted by Mylan Pharmaceuticals Inc. on its Acyclovir 200 mg capsule, Lot #2A005D, comparing to Zovirax^{R} 200 mg capsule, lot #3Z2158, manufactured by Burroughs Wellcome Co., have been found acceptable by the Division of Bioequivalence. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of distilled water at 37° using USP 23 apparatus 1 (basket) at 100 rpm. The test products should meet the following specifications:

   Not less than [redacted] of the labeled amount of acyclovir in the dosage form is dissolved in 30 minutes.

3. From the bioequivalence point of view, Mylan Pharmaceuticals, Inc. has met the requirements of *in vivo* bioequivalence and *in vitro* dissolution testing and the application is approvable.

5/15/96

Lin-whei Chuang
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG

5/15/96

Con__ Date: 5/20/96

Keith Chan, Ph.D.
Director, Division of Bioequivalence

cc: ANDA 74-727 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-344 (Cviswanathan), HFD-652 (Huang, Chuang), Drug File, Division File

First Draft LWC 05/14/96 c:\wpfiles\74-727a.296
Final Pink LWC 05/15/96 x:\new\firmsam\mylan\ltrs&rev\74727a.296

D W

MAY 9 1996

Acyclovir
200 mg Capsule
ANDA 74-727
Reviewer: L. Chuang

Mylan Pharmaceuticals Inc.
Morgantown, WV
Submission Date:
December 7, 1995

Review of a Bioequivalence Study -- (Food Study)

Introduction:

A bioequivalence study was previously conducted by the firm in fasting subjects and was found to be incomplete by the Division of Bioequivalence due to two deficiencies (see letter of 02/06/96 from the Division). It was also recommended to the firm that a limited food study with a three-way [redacted] crossover design is be conducted for the approval of the ANDA. The present submission contains a food study which was conducted before the receipt of the Division's letter of 02/06/96.

Bioequivalence Study -- Limited Food Study

The objective of this study was to compare the bioavailability of Mylan's acyclovir 200 mg capsules and Burroughs Wellcome's Zovirax[R] 200 mg capsules under post-prandial conditions. The effect of food on the absorption of the test formulation was also evaluated.

The clinical study was conducted in the facilities of
during the time period of 05/28-06/12/95 by
The analytical study was conducted at Mylan Pharmaceuticals Inc. in Morgantown, WV during the time period of 06/14-08/22/95 by P.K. Noonan, Ph.D..

The study design was an open-label, randomized, single-dose, 3-way crossover in non-fasting and fasting male volunteers. The protocol and the informed consent form were approved by the institutional Review Board (chaired by on 05/11/95.

Of the 22 subjects recruited, 17 subjects completed all phases of the study. Only the demographics of these 17 subjects were reported. They were 19-38 years old and consisted of 15 white and 2 black males. The inclusion criteria applied during the screening procedure conducted within 1 week of the initiation of the study were:

1. male, 18-45 years old, within ±10% of ideal body weight according to Metropolitan Life Insurance Bulletin, 1983 and at least 60 Kg.
2. non-tobacco-user.
3. Normal results of physical examination, laboratory evaluations and 12-lead ECG, according to the *Guide for Clinically Relevant Abnormalities*, performed within 14 days in the initial dose of study medication.

The exclusion criteria were:

1. history of any chronic disease, drug and/or alcohol abuse, or use of any psychotropic agents.
2. Acute illness or surgery during the 4 weeks prior to the study
3. loss of a significant amount of blood or plasma (>450 mL) within 30 days prior to the study.
4. receipt of an investigational drug within 28 days prior to the study.

All volunteers were instructed not to take any concurrent medications from 14 days before the study until the end of the study, and not to take any alcohol- caffeine- or xanthine-containing foods or beverages, or any vitamins within 48 hours prior to the initial dose of the study medication. They entered the clinical site in the evening before dosing for a supervised overnight fast before subjectings to one of the following treatments randomly assigned:

Treatment A - Test Drug: Acyclovir capsules, 2 x 200 mg, Mylan Pharmaceutical lot #2A005D, potency 98.8%, release date 10/04/94, lot size [redacted] capsules, given 30 minutes after a standard breakfast*

Treatment B - Reference Drug: Zovirax® capsules, 2 x 200 mg, Burroughs Wellcome lot #3Z2158, potency 99.6%, expires 01/97, given 30 minutes after a standard breakfast

Treatment C - Test Drug: Acyclovir capsules, 2 x 200 mg, Mylan Pharmaceutical lot #2A005D, potency 98.8%, release date 10/04/94, lot size [redacted] capsules, given under fasting condition

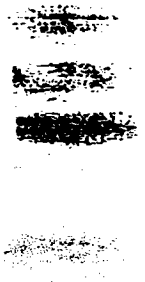
* = 1 buttered English muffin, 1 fried egg, 1 slice of Canadian bacon, 1 slice of American cheese, 1 serving of hashed brown potatoes, 6 ounces of orange juice and 8 ounces of whole milk.

Each treatment was taken with 240 mL of water. Water was not permitted for 2 hours before and 2 hours after dosing. Subjects remained fasted for 5 hours until standard meals were provided at 5 and 10 hours after dosing and at appropriate time thereafter. Subjects engaged in normal activities for the first 8 hours after dosing, avoiding both vigorous exertion and complete rest. There was a 7-day washout period between treatments.

Blood samples (10 mL each) were collected into heparinized tubes at 0, 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, and 24 hours after dosing. Plasma samples were prepared and stored at -20°C.

At the conclusion of the study, on 06/12/95, all subjects had a physical examination including blood and urine analysis.

Analytical Method -- **Not for Release through FOI**:



Results:

Of the 22 subjects recruited, 5 failed to report on the evening prior to phase 1 dosing. The final clinical evaluation and clinical laboratory results in all subjects did not show any clinically significant abnormalities. Only 1 adverse event was reported: subject #7 experienced stomach pain and diarrhea headache during phase 3, treatment C.

The plasma samples from 17 subjects were assayed for acyclovir. Among the 867 study samples analyzed, 13 samples were repeated, none of them had any initial value and were repeated due to outside standard curve range, loss during extraction, poor chromatography or abnormal internal standard response.

The mean plasma concentrations of acyclovir at each sampling point after each treatment and the mean pharmacokinetic parameters are presented below in Table 1 and in the attached Figures 1 [illegible]

Table 1: Mean (C.V.%) Plasma Acyclovir Concentrations (ng/mL) at Each Sampling Time Point and the Mean Pharmacokinetic Parameters (n = 17)

Time (hour)	Mylan - Non-Fasting (Treatment A)	Burroughs Wellcome - Non-Fasting (Treatment B)	Mylan - Fasting (Treatment C)
0	0	0	0
0.33	0	0	43.28 (32)
0.67	25.27 (43)	37.88 (27)	51.23 (17)
1	126.43 (35)	167.74 (19)	426.13 (9.4)
1.33	292.47 (22)	354.12 (14)	462.35 (7.5)
1.67	451.89 (17)	511.72 (11)	456.21 (9.7)
2	529.45 (12)	607.92 (9.7)	461.16 (10)
2.5	624.73 (14)	664.96 (6.2)	424.88 (13)
3	610.87 (6.8)	631.91 (5.1)	367.56 (14)
4	516.89 (7.5)	534.77 (4.7)	271.40 (14)
5	418.40 (8.0)	427.23 (5.4)	219.02 (15)
6	309.75 (6.6)	308.37 (4.8)	160.14 (12)
8	178.35 (45)	171.35 (5.7)	104.23 (11)

10	106.28 (5.1)	103.26 (4.6)	66.13 (9.2)
12	65.79 (5.2)	68.45 (5.1)	47.14 (7.8)
16	32.79 (5.1)	35.87 (4.8)	29.93 (6.0)
24	16.23 (11)	16.29 (10)	18.53 (7.0)
AUC_{0-t} (ng*hr/mL)	3707 (22)	3865 (15)	2711 (37)
AUC_{0-inf} (ng*hr/mL)	3882 (22)	4036 (15)	2985 (34)
C_{max} (ng/mL)	724.30 (24)	736.34 (22)	563.30 (40)
$LNAUC_{0-t}$	8.1956 (3625*)	8.2479 (3819*)	7.8481 (2561*)
$LNAUC_{0-inf}$	8.2418 (3796*)	8.2919 (3991*)	7.9524 (2842*)
LNC_{max}	6.5528 (701.25*)	6.5777 (718.87*)	6.2630 (540.76*)
T_{max} (hour)	2.58 (29)	2.66 (28)	1.45 (38)
$T_{1/2}$ (hour)	6.38 (25)	6.22 (22)	9.77 (29)

* = Geometric mean

The ratios of pharmacokinetic parameters among the 3 treatments are presented below:

Table 2: Ratios of Pharmacokinetic parameters

Parameter	Treatment A / Treatment B		Treatment A / Treatment C	
	Arithmetic Means Ratio	Geometric Means Ratio	Arithmetic Means Ratio	Geometric Means Ratio
AUC_{0-t}	0.96	0.95	1.38	1.41
AUC_{0-inf}	0.96	0.95	1.30	1.33
C_{max}	0.98	0.97	1.29	1.30
T_{max}	0.97	----	1.78	----
$T_{1/2}$	1.03	----	0.65	----

Figure 1

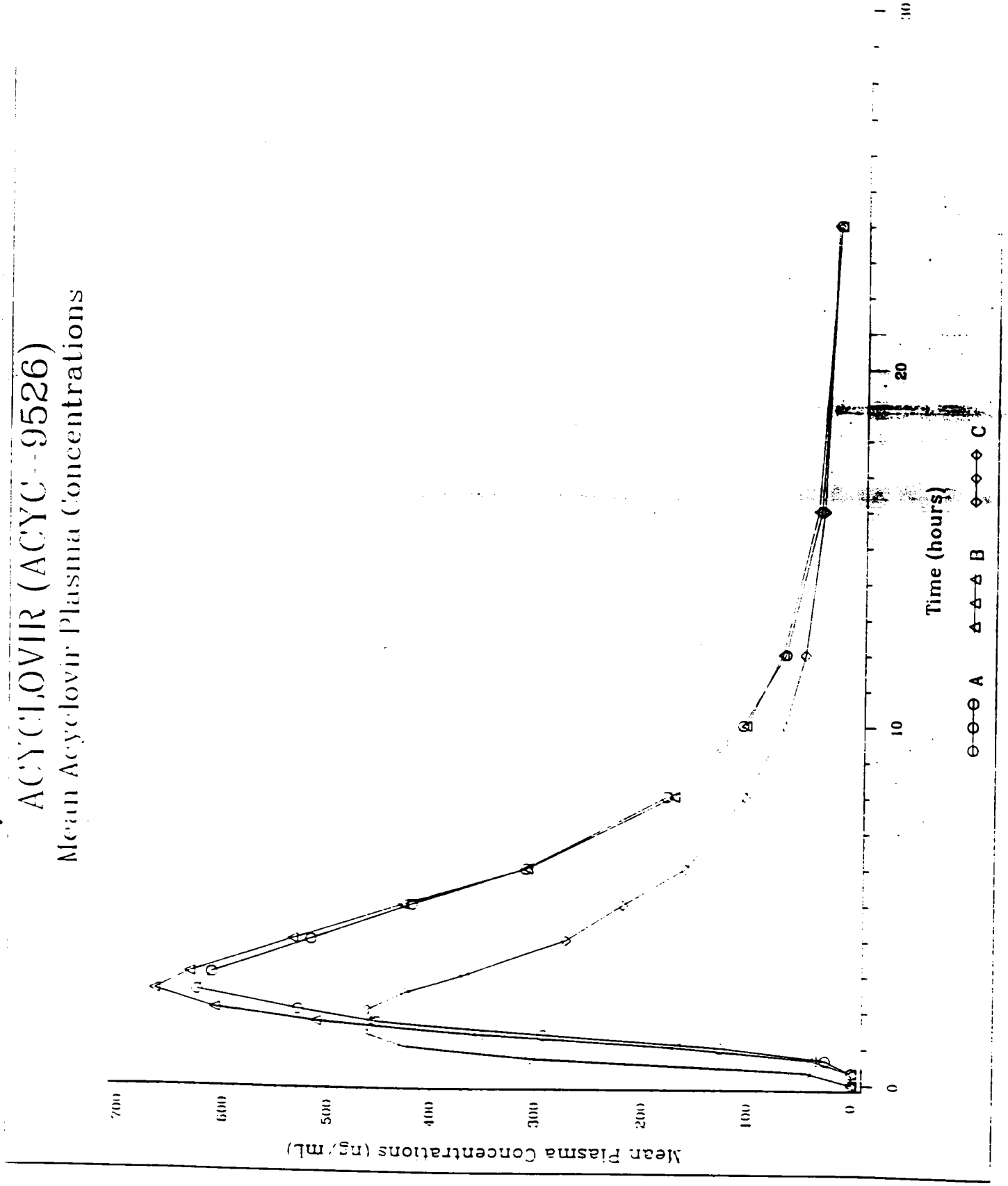
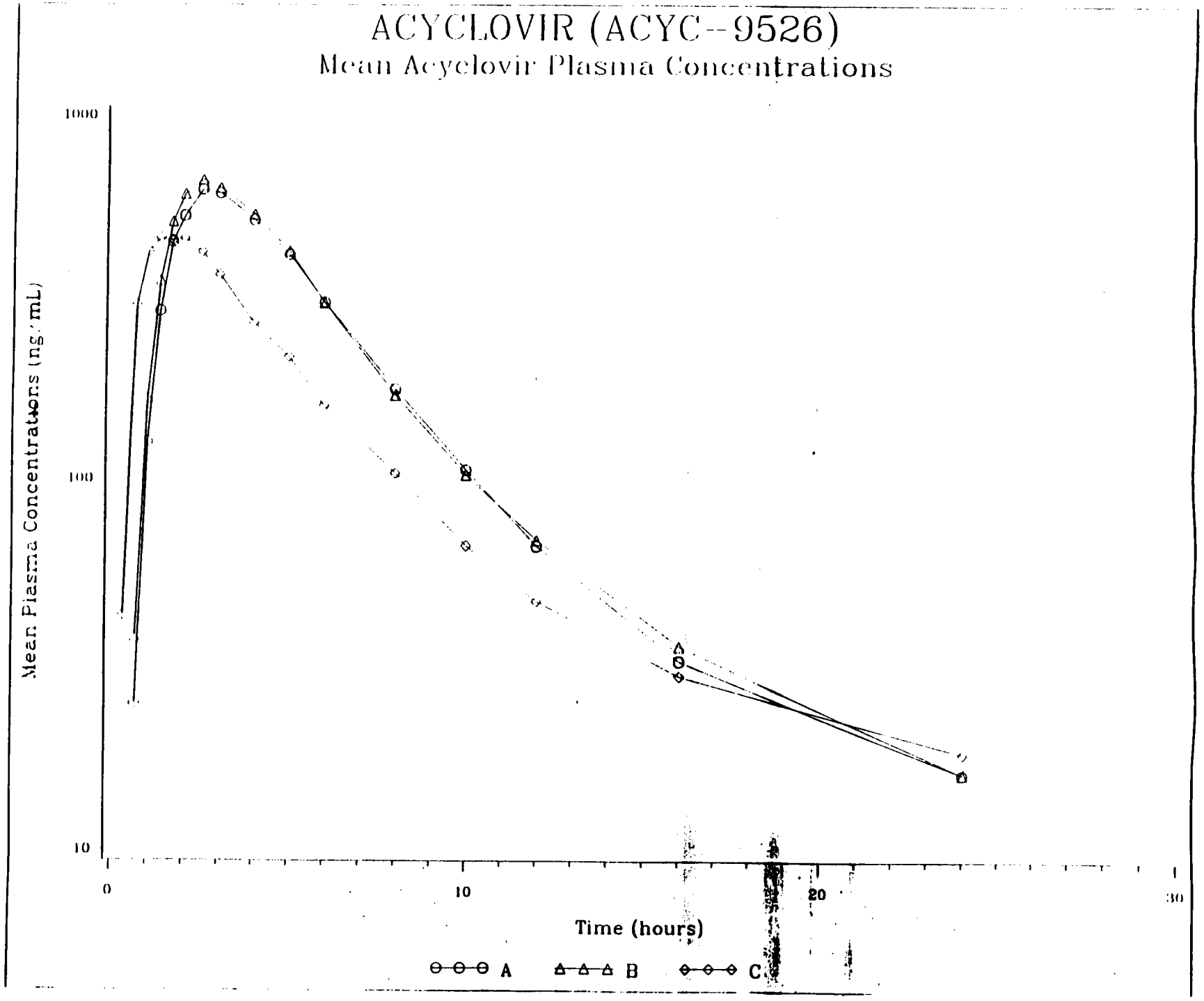


Figure 1

Figure 2


ACYCLOVIR (ACYC--9526)
Mean Acyclovir Plasma Concentrations
Mean Plasma Concentrations (ng/mL)
1000
100
10
0
10
20
30
Time (hours)
A
B
C

Comments:

1. The test formulation and the reference formulation were absorbed at almost the same rate (mean C_{max}) and to almost the same extent (mean AUC_{0-t} and mean AUC_{0-inf}) under post-prandial condition.

2. When comparing the test product with and without food, the mean AUC was increased by 30-41%, the mean C_{max} was increased by 29-30%, the mean T_{max} was delayed by 1.1 hours and the $T_{1/2}$ was lengthen by 3.4 hours. This seems to be contrary to the labeling statement that "the influence of food on the absorption of acyclovir was not apparent".

3. Ratios of the means of AUC_{0-t}, AUC_{0-inf} and C_{max} for the test product given after food versus reference product given after food were all within the 0.8-1.2 limit.

4. The method and results of the study are acceptable.

5. The formulation information and dissolution data are the same as submitted previously with the results of bioequivalence study under fasting condition.

Recommendation:

The non-fasting bioequivalence study conducted by Mylan Pharmaceuticals Inc. on its Acyclovir 200 mg capsule, Lot #2A005D, comparing to Zovirax^R 200 mg capsule, lot #3Z2158, manufactured by Burroughs Wellcome Co. has been found acceptable by the Division of Bioequivalence. The study demonstrated that Mylan's acyclovir 200 mg capsule is bioequivalent to the reference product, Zovirax^R 200 mg capsule manufactured by Burroughs Wellcome Co. when administered under non-fasting condition.

4/26/96

Lin-whei Chuang
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG
Concur_ Date: 5/9/96

5/3/96

Kenli Chan, Ph.D.
Director, Division of Bioequivalence

cc: ANDA 74-727 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-344 (Cviswanathan), HFD-652 (Huang, Chuang), Drug File, Division File

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Final Draft LWC 04/26/96 x:\new\firmsam\mylan\ltrs&rev\74-727s.d95

D,J

ANDA 74-727

FEB -6 1996

Mylan Pharmaceuticals Inc.
Attention: Patrick K. Noonan, Ph.D.
781 Chestnut Ridge Road
P.O. BOX 4310
Morgantown WV 26504-4310

Dear Sir:

Reference is made to the Abbreviated New Drug Application submitted on August 10, 1995, for Acyclovir Capsules 200 mg.

The Office acknowledge receipt of your amendment (the results of non-fasting study) dated December 7, 1995, which will be reviewed according to Agency policy.

The Office of Generic Drugs has reviewed the bioequivalence data submitted and the following comments are provided for your consideration:

1. The time period of medication and diet restrictions listed in the protocol should be provided. An explanation for the 5 subjects who did not complete the study should also be provided.

2. Please provide pre-study validation data for the assay methodology of acyclovir.

3. The information should be provided on the assay methodology conducted for the dissolution tests and change the specification of the dissolution test to "not less than dissolved in 30 minutes".

4. A limited food study should be conducted with a three-way crossover design in at least 18 subjects using all six possible dosing sequences. The three treatments are:

   1) test product with food;
   2) reference product with food; and
   3) test product fasting

   For the two non-fasting treatments, the following standard meal should be used:

   one fried egg
   one slice of American cheese
   one slice of Canadian bacon
   one buttered English muffin

one serving of hash brown potatoes
240 mL of whole milk and
180 mL of orange juice

The meal should be completed within 30 minutes, and the dose given 30 minutes after the meal is begun and taken with 240 mL of water.

5. Please be advised that at the time of filing an application should be essentially complete include both fasting and non-fasting studies. In the future you may contact the Division of Bioequivalence during your drug development program for advice on the required studies.

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter. Should you have any questions, please call Jason A. Gross, Pharm.D., at (301) 594-2290. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

Keith K. Chan, ~~Ph.D~~.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation
and Research

D. J

JAN 25 1996

Acyclovir
200 mg Capsule
ANDA 74-727
Reviewer: L. Chuang

Mylan Pharmaceuticals Inc.
Morgantown, WV
Submission Date:
August 10, 1995

Review of a Bioequivalence Study and Dissolution Data

Introduction:

Acyclovir is 9-[(2-hydroxyethoxy)methyl]guanine, a synthetic purine nucleoside with antiviral activity against human herpes viruses, including herpes simplex types 1 (HSV-1) and 2 (HSV-2), varicella zoster virus (VCV), Epstein-Barr virus (EBV), and cytomegalovirus (CMV). The viral inhibitory activity is highly selective, involving preferential uptake into virus-infected cells and requiring a virus-specific thymidine kinase for conversion to the monophosphate. Subsequent conversion to the triphosphate results in irreversible binding to DNA polymerase and termination of DNA replication. Acyclovir is indicated for: 1) capsules and suspension - treatment of initial episodes and management of recurrent episodes of genital herpes in certain patients; 2) capsules, tablets, and suspension - acute treatment of herpes zoster and chicken pox.

Acyclovir is marketed as Zovirax (Burroughs-Wellcome) 200 mg capsules (NDA #18-828, 1/25/85), 800 and 400 mg tablets (NDA #20-089, 4/30/91), and oral suspension 200 mg/5 mL (NDA #19-909, 12/22/89).

Pharmacokinetics

The oral absorption of acyclovir is slow, variable, and incomplete, with absolute bioavailability estimated as 15-30% from different studies involving both normals and patients. Reported values for C_{max} and T_{max} in healthy subjects after a 200 mg capsule were 0.3 ± 0.1 mg/L and 1.5-2.5 hours, respectively. Several studies in healthy volunteers have demonstrated dose-dependent absorption: (1) fraction of the dose recovered unchanged in the urine decreased over the dosing range of 100-600 mg (13.2% of a 100 mg dose; 12.1%, 200 mg; 7.4%, 400 mg; 6%, 600 mg dose); (2) mean C_{MAX} was 0.58 mg/L after a single 600 mg dose and 0.50 mg/L after a single 200 mg dose; (3) mean AUC after a 600 mg dose given as divided doses every four hours, was about three times higher than after a single 600 mg dose; and (4) mean AUC from a 400 mg dose given as a duodenal infusion was about 1.7 times that from tablets, which suggested capacity-limited absorption. However, the results of one multiple dose study (200 mg q4h vs. 3 X 200 mg q4h) in immunocompromised patients suggested that net absorption of

acyclovir is nearly proportional to dose in the 200-600 mg dose range.

Plasma elimination of acyclovir is biphasic with a beta phase half-life of 2-3 hours. Renal excretion is the major route of elimination with 45-79% of a dose recovered unchanged in the urine. After an intravenous infusion of a ^{14}C tracer dose in patients, 71-99% of the dose was recovered in the urine. There is only one significant, inactive metabolite, 9-carboxymethoxymethyl guanine (CMMG), which accounts for 8-14% of a dose.

Bioequivalence Study -- Fasting

The objective of this study was to compare, in fasting volunteers, the bioavailability of Mylan's acyclovir 200 mg capsules and Burroughs Wellcome's Zovirax® 200 mg capsules following the administration of a 400 mg dose (2 capsules).

The clinical study was conducted in the facilities of during the time period of 02/25-03/05/95 by . The analytical study was conducted at Mylan Pharmaceuticals Inc. in Morgantown, WV during the time period of 03/28-04/27/95 by P.K. Noonan, Ph.D..

The study design was an open-label, randomized, single-dose, 2-way crossover in fasting male volunteers. The protocol and the informed consent form were approved by the Institutional Review Board (chaired by on 02/16/95.

Of the 41 subjects recruited, 36 subjects completed both phases of the study. Only the demography of these 36 subjects were reported. They were 18-27 years old and consisted of 34 white and 2 Asian-Pacific males. The inclusion criteria applied during the screening procedure conducted within 1 week of the initiation of the study were:

1. male, 18-45 years old, within ±10% of ideal body weight according to Metropolitan Life Insurance Bulletin, 1983.
2. nonsmokers or at least 6 months since cessation of smoking
3. laboratory evaluations within ±10% of normal limits (except clinically irrelevant parameters e.g., cholesterol) which included blood count, differential and platelets, liver function tests, kidney function tests, uric acid, cholesterol, iron, hepatitis B surface antigen, human HIV, urinalysis and drug screen.

The exclusion criteria were:

1. history or presence of significant disease of any organs.
2. alcoholism, drug abuse, or hypersensitivity to acyclovir.
3. abnormal diet during the 4 weeks preceding the study.
4. donation of more than 450 mL of blood or plasma within 4 weeks of the study.
5. participation in another clinical trial within 28 days of the start of the study.

All volunteers were instructed not to take any concurrent medications and not to take any alcohol- or xanthine-containing foods or beverages, however, the firm did not specify the time period of such restrictions. They entered the clinical site in the evening of 02/24/95 for a supervised overnight fast before subjecting to one of the following treatments randomly assigned:

Treatment A - Test Drug: Acyclovir capsules, 2 x 200 mg, Mylan Pharmaceutical lot #2A005D, potency 98.8%, release date 10/04/94, lot size capsules

Treatment B - Reference Drug: Zovirax® capsules, 2 x 200 mg, Burroughs Wellcome lot #3Z2158, potency 99.6%, expires 01/97

Each treatment was taken with 240 mL of water. Water was not permitted for 2 hours before and 4 hours after dosing. Subjects remained fasted for 5 hours until standard meals were provided at 5 and 10 hours after dosing and at appropriate time thereafter. Subjects engaged in normal activities for the first 12 hours after dosing, avoiding both vigorous exertion and complete rest. After a 7-day washout, on 03/04/95, each subject was crossed over to the alternative treatment.

Blood samples (10 mL each) were collected into Vacutainers containing EDTA at -0.5, 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, and 24 hours after dosing. Plasma samples were prepared and stored at -20°C.

At the conclusion of the study, on 03/05/95, all subjects had a physical examination including blood and urine analysis.

Analytical Method -- **Not for Release through FOI.**

Results:

Thirty-six (36) subjects completed the study without any protocol deviation. The firm however did not explain why 5 out of the 41

subjects recruited did not complete the study.

Only 1 adverse event was reported; subject #3 experienced headache during period 1, treatment A.

The results of the physical examination at the conclusion of the study revealed no changes from the entrance physical examination.

The plasma samples from 36 subjects were assayed for acyclovir. Among the 1224 study samples analyzed, 20 samples were repeated. One (1) was repeated due to instrument malfunction and the rest were repeated because the original results were above the standard curve range (>1000 ng/mL).

The mean plasma concentrations of acyclovir at each sampling point after both treatments and the mean pharmacokinetic parameters are presented below in Table 1.

Table 1: Mean (C.V.%) Plasma Acyclovir Concentrations (ng/mL) at Each Sampling Time Point and the Mean Pharmacokinetic Parameters (n = 36)

Time (hour)	Mylan (Treatment A)	Burroughs Wellcome (Treatment B)
0	0	0
0.33	42.19 (116)	38.40 (138)
0.67	369.45 (56)	355.29 (48)
1.00	526.36 (35)	577.11 (33)
1.33	593.63 (30)	660.14 (30)
1.67	584.49 (33)	618.26 (30)
2.00	581.13 (31)	593.51 (33)
2.50	547.55 (36)	527.44 (31)
3.00	512.57 (41)	480.02 (36)
4.00	396.59 (45)	389.20 (39)
5.00	298.20 (41)	292.90 (38)
6.00	231.02 (50)	222.12 (41)
8.00	146.12 (45)	137.31 (45)
10.00	103.04 (46)	94.94 (33)
12.00	68.46 (43)	70.35 (40)

16.00	42.10	(38)	48.11	(68)
24.00	23.10	(54)	22.46	(42)
AUC_{0-t} (ng*hr/mL)	3682.65	(32)	3683.54	(30)
AUC_{0-inf} (ng*hr/mL)	3983.11	(30)	3960.39	(28)
C_{max} (ng/mL)	727.53	(23)	732.76	(26)
$LNAUC_{0-t}$	8.160632, 3500.40[a]		8.165650, 3518.01[a]	
$LNAUC_{0-inf}$	8.243612, 3803.25[a]		8.245343, 3809.84[a]	
LNC_{max}	6.560169, 706.39[a]		6.558414, 705.15[a]	
T_{max} (hour)	1.7592	(47)	1.5647	(42)
$T_{1/2}$ (hour)	7.7542	(35)	7.5669	(32)

a = geometric mean

Analysis of Variance was performed using SAS GLM procedure. The model included sequence, subject within sequence, treatment and period as factors. The sequence effect was tested using the subjects within sequence effect as the error term. The treatment and period effect were tested against the residual mean square error. Slightly significant period effects were detected for AUC_{0-t}, AUC_{0-inf}, $LNAUC_{0-t}$, and $LNAUC_{0-inf}$ (p=0.02-0.04).

The LS means of the non-transformed and log-transformed pharmacokinetic parameters, ratios of these means and the 90% confidence intervals of test product versus reference product are presented in Table 2.

Table 2: Statistical Analysis - Acyclovir (n=36)

Parameter	LS Means (Test)	LS Means (Reference)	T/R	90% Confidence Interval
AUC_{0-t}	3682.65	3683.54	1.00	(0.925; 1.075)
$LNAUC_{0-t}$	8.16063 (3500.40[a])	8.16565 (3518.01[a])	0.99[c]	(0.912; 1.086)
AUC_{0-inf}	3983.11	3960.39	1.01	(0.936; 1.075)
$LNAUC_{0-inf}$	8.243612 (3803.25[a])	8.245343 (3809.84[a])	1.00[c]	(0.922; 1.081)
C_{max}	727.53	732.76	0.99	(0.927; 1.058)

LNC_{max}	6.560169 (706.39[a])	6.558414 (705.15[a])	1.00[b]	(0.927; 1.081)

a = Geometric Mean
b = Ratio of Geometric Means

Comments:

1. The firm did not specify the time period of medication and diet restrictions in the protocol or explain in the result section why 5 out of the 41 subjects recruited did not complete the study.

2. The firm did not present any pre-study validation data for the analytical methodology.

3. The elimination half-lives observed in this study (2.92-14.05 hours with mean of 7.66 hours) were longer than those reported in the literatures (2-3 hours).

4. The formula for the calculation of confidence intervals (CIs) presented on page 585 of the submission is incorrect due to the following two reasons:

   a. The firm left out the adding of 1.0:

      % CI = 100 X (1.0 + CI/least square mean of reference)

   However, the 90% CIs of all non-transformed data submitted by the firm were calculated based on this correct formula.

   b. The formula is not appropriate for log-transformed data although the 90% CIs of the log-transformed data submitted by the firm were calculated based on the correct formula as following:

      CI = 100 X Antilog [Estimate ± (Std. Err. of Estimate X t)]

5. Both test and reference drugs produced peak concentrations between 0.67-4.0 hours with comparable mean T_{max} (see Table 1).

   The AUCs and C_{max}s of both drugs were almost identical (ratios of T/R=0.99-1.00). The 90% CIs for $LNAUC_{0-t}$, $LNAUC_{0-inf}$ and LNC_{max} of the test drug remained within the 80-125% limit of the corresponding reference mean values.

Formulation - Not for Release through FOI:

The formulation of the test product was provided by the firm and presented below:

Ingredient	mg/tablet (range)
Acyclovir	200.0 (200.0-218.0*)
Pregelatinized Starch	
Sodium Lauryl Sulfate	
Magnesium Stearate/ Sodium Lauryl Sulfate	
Colloidal Silicon Dioxide	
Total	380.0

*Based upon the potency factor of the acyclovir raw material
**Adjusted to compensate differences in the Acyclovir quantity

Dissolution Testing:

The firm conducted comparative dissolution tests on the test and reference drugs used in the above bioequivalence study. The results are presented below in Table 3.

Table 3 - In Vitro Dissolution Testing

Drug (Generic Name): Acyclovir
Dosage Form: Capsule
Dose Strength: 200 mg
ANDA No.: 74-727
Firm: Mylan Pharmaceuticals Inc.
Submission Date: 8/10/95

I. Conditions for Dissolution Testing:

USP XXIII Apparatus: Basket RPM: 100
No. Units Tested: 12
Medium: Distilled Water Volume: 900 mL
Tolerance: NLT (Q) in 30 minutes
Reference Drug: Zovirax® (Burroughs Wellcome)
Assay Methodology: not given

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # 2A005D Strength (mg): 200			Reference Product Lot # 3Z2158 Strength (mg): 200		
	Mean %	Range	%CV	Mean %	Range	%CV
10	48		24.6	60		27.8
20	96		2.8	92.2		7.1
30	100		2.0	94.1		4.1

Comments:

1. The firm did not provide information on the assay methodology for dissolution tests.

2. The specification for the results of dissolution tests using the above method for acyclovir tablets is "not less than dissolved in 30 minutes" according to FDA's "Handbook of Drug Dissolution Standards". No dissolution method is available in USP at present. However, the firm's specification was "not less than % dissolved in 30 minutes".

General Comment:

An acceptable limited food study, using the same batches of test and reference products as those used in the acceptable fasting study, must be conducted as a condition for product approval due to the following reasons:

1. The labeling of the reference drug, Zovirax®, states that "the influence of food on the absorption of acyclovir was not apparent".

2. Acyclovir is indicated to be administered up to 5 times a day, it is likely to be taken with food.

Deficiencies:

1. The firm should provide the time period of medication and diet restrictions in the protocol and explanation for the 5 subjects who did not complete the study.

2. The firm should provide pre-study validation data for the assay methodology of acyclovir.

3. The firm should provide information on the assay methodology conducted for the dissolution tests and change the specification of the dissolution test to "not less than dissolved in 30 minutes".

4. The firm should conduct a limited food study with a three-way crossover design in at least 12 subjects using all six possible dosing sequences. The three treatments are: 1) test product with food; 2) reference product with food; 3) test product fasting. For the two non-fasting treatments, the following standard meal should be used: one fried egg, one slice of American cheese, one slice of Canadian bacon, one buttered English muffin, one serving of hash brown potatoes, 240 mL of whole milk, and 180 mL of orange juice. The meal

should be completed within 30 minutes, and the dose given 30 minutes after the meal is begun and taken with 240 mL of water.

Recommendation:

1. The bioequivalence study conducted by Mylan Pharmaceuticals Inc. on its Acyclovir 200 mg capsule, Lot #2A005D, comparing to Zovirax[R] 200 mg capsule, lot #3Z2158, manufactured by Burroughs Wellcome Co., in fasting volunteers, have been found incomplete due to deficiencies #1-2.

2. The dissolution tests conducted by Mylan Pharmaceuticals Inc. on its Acyclovir 200 mg capsule, Lot #2A005D, comparing to Zovirax[R] 200 mg capsule, lot #3Z2158, manufactured by Burroughs Wellcome Co., have been found incomplete by the Division of Bioequivalence due to deficiency #3.

3. The firm should conduct a limited food study as described in deficiency #4.

4. In future applications, the report of fasting study and the limited food study should be submitted at the same time.

The above deficiencies and recommendations should be forwarded to the firm.

1/25/96

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Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG 1/25/96

cc: ANDA 74-727 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-344 (Cviswanathan), HFD-652 (Huang, Chuang), Drug File, Division File

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